AMENDMENTS TO THE SPECIFICATION

Please amend the paragraphs beginning on page 1, line 34 as follows:

An inhibitory action of certain oncostatic agents such as ~~tamoxoifen [sic]~~tamoxifen on the migration and invasion of cancer cells is known [J Clin Endocrinol Metab 1995 Jan.; 80(1) : 308-13].

The inhibition of tumor cell invasion by verapamil has been reported [Pigment Cell Res 1991 Dec.; 4(5-6) : 225-33[[.]]].

The influence of ~~melantonin [sic]~~melatonin on invasive and metastatic properties of MCF-7 human breast cancer cells has been reported [Cancer res 1998 Oct. 1; 58(19) : 4383-90].

Please amend the paragraphs beginning on page 3, line 13 as follows:

It has surprisingly been found that the N-substituted indole-3-~~gloxylamides [sic]~~glyoxylamides described in German Patent Application 19814 838.0, of the general formula 1 described below, which are suitable for the treatment of oncoses, further have those advantageous properties for tumor treatment which can extend there area of use.

The invention relates to the use of N-substituted indole-3-~~gloxylamides [sic]~~glyoxylamides according to claim 1 ~~general formula 1a~~ for tumor treatment in particular in the case of pharmaceutical resistance and metastasizing carcinoma and for the suppression of mestastasis formation, and also as angiogenesis inhibitors,

Please amend the paragraph beginning on page 4, line 10 as follows:

R is further selected from the benxyloxycarbonyl group (Z group), ~~and~~ the tertiary-butoxycarbonyl radical (BOC radical), ~~furthermore~~ and the acetyl group;[[.]]

Please amend the paragraph beginning on page 4, line 13 as follows:

R_1 can be ~~the~~ a phenyl ring, which is mono- or polysubstituted by (C_1-C_6)-alkyl, (C_1-C_6)-alkoxy, cyano, halogen, trifluoromethyl, hydroxyl, benzyloxy, nitro, amino, (C_1-C_6)-alkylamino, (C_1-C_6)-alkoxycarbonylamino ~~and~~ or by the carboxyl group or by the carboxyl group esterified with C_1-C_6-alkanols, or R_1 can be a pyridine structure of the formula 2 ~~and its N-oxide[sic]~~

Please amend the paragraph beginning on page 5, line 1 as follows:

R_1 can further be a 2- or 4-pyrimidinyl heterocycle, where the 2-pyrimidinyl ring can be mono- or polysubstituted by ~~the~~ a methyl group, ~~furthermore are [sic] the~~ a 2-, 3-, ~~and~~ 4- ~~and~~ or 8-quinolyl structure may be substituted by (C_1-C_6)-alkyl, halogen, ~~the~~ a nitro group, ~~the~~ a amino group ~~and~~ or ~~the~~ a (C_1-C_6)-alkylamino radical, ~~are [sic]~~ a 2-, 3-, ~~and [sic]~~ or 4-quinolylmethyl group, where the ring carbons of the pyridylmethyl radical of the quinolyl group and of the quinolylmethyl radical can be substituted by (C_1-C_6)-alkyl, (C_1-C_6)-alkoxy, nitro, amino and (C_1-C_6)-alkoxycarbonylamino.

Please amend the paragraph beginning on page 4, line 25 as follows:

and its N-oxide, where the pyridine structure is alternatively bonded to the ring carbon atoms 2, 3, ~~and~~ or 4 and can be substituted by the substituents R_5 and R_6. The radicals R_5 and R_6 can be identical or different and have the meaning (C_1-C_6)-alkyl ~~and the meaning~~ (C_3-C_7)-cycloalkyl, (C_1-C_6)-alkoxy, nitro, amino, hydroxyl, halogen ~~and~~ trifluoromethyl, ~~and further are the~~ ethoxycarbonylamino radical ~~and~~ or the group carboxyalkyloxy in which the alkyl group can have 1-4 C atoms.

Please amend the paragraph beginning on page 5, line 1 as follows:

R_1 can further be a 2- or 4-pyrimidinyl heterocycle, where the 2-pyrimidinyl ring can be mono- or polysubstituted by the methyl group; ~~, furthermore are [sic]~~ a ~~the~~ 2-, 3-, ~~and~~ 4- ~~and~~ or 8-quinolyl structure substituted by (C_1-C_6)-alkyl, halogen, the nitro group, the amino group ~~and~~ or the (C_1-C_6)-alkylamino radical; ~~are~~ or ~~[sic]~~ a 2-, 3- ~~and~~ or a ~~[sic]~~ 4-quinolylmethyl group, where the

ring carbons of the pyridylmethyl radical of the quinolyl group and of the quinolylmethyl radical can be substituted by (C_1-C_6)-alkyl, (C_1-C_6)-alkoxy, nitro, amino, ~~and~~ or (C_1-C_6)-alkoxycarbonylamino.

Please amend the paragraph beginning on page 5, line 19 as follows:

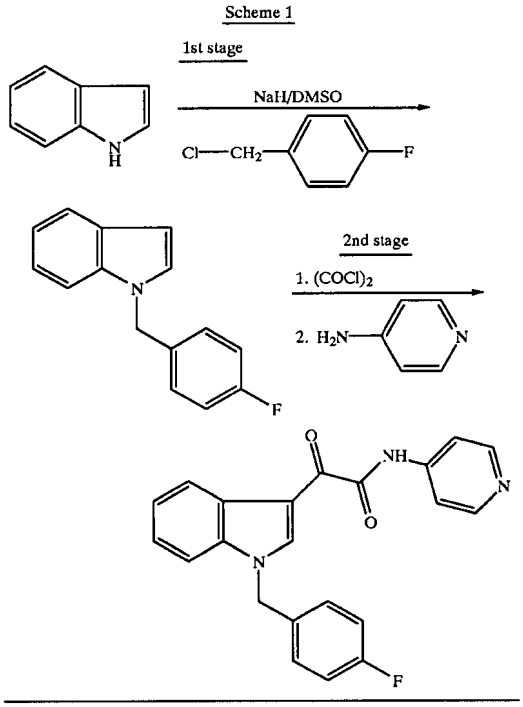
–CH_2COOH; -$CH(CH_3)$-COOH; $(CH_3)_2$-CH-$(CH_2)_2$-CH-COO-; H_3C-H_2C-$CH(CH_3)$-[[ ]]CH(COOH)-~~[sic]~~; HO-H_2C-CH(COOH)-; phenyl-CH_2CH(COOH)-; (4-imidazolyl)-CH_2-CH-(COOH)-; HN=$C(NH_2)$-NH-$(CH_2)_3$-CH(COOH)-; H_2N-$(CH_2)_4$-CH(COOH)-; H_2N-CO-CH_2-CH-(COOH)-; and HOOC-$(CH_2)_2$-CH(COOH)-

Please amend the paragraph beginning on page 6, line 14 as follows:

R_7 is an alkyl radical, is a phenyl ring which can be mono- or polysubstituted by (C_1-C_6)-alkyl, (C_1-C_6)-alkoxy, halogen, ~~the~~ a nitro group, ~~the~~ an amino function ~~and~~ or by the (C_1-C_6)-alkylamino group. R_7 is furthermore ~~the~~ a benzhydryl group ~~and the~~ or a bis-p-~~fluorobenzylhydryl [sic]~~fluorobenzhydryl group.

Please amend the paragraph beginning on page 8, line 23 as follows:

The preparation processes for the substances can be taken from the examples of German Patent DE 196 36 150 A1. The compounds of general formula I are obtainable according to the following Scheme 1, shown for the synthesis of the compound of Example 1:



General Procedure for the Preparation of the Compounds of the General Formula I According to Scheme 1

1st Stage

The indole derivative, which can be unsubstituted or mono- or polysubstituted on C-2 or in the phenyl structure, is dissolved in a protic, dipolar aprotic or nonpolar organic solvent, such as, for example, isopropanol, tetrahydrofuran, dimethyl sulfoxide, dimethylformamide, dimethylacetamide, N-methylpyrrolidone, dioxane, toluene or methylene chloride and added dropwise to a suspension of a base in a molar or excess amount prepared in a 3-necked flask under an N_2 atmosphere, such as, for example, sodium hydride, powdered potassium hydroxide, potassium tert-butoxide, dimethylaminopyridine, or sodium amide in a suitable solvent. The desired alkyl, aralkyl or heteroalkyl halide, if appropriate with addition of a catalyst, such as, for example, copper, is then added and the mixture is reacted for some time, for example, 30 minutes to 1.2 hours, and the temperature is kept within a range from 0 °C to 120 °C, preferably between 30 °C and 80 °C, particularly between 50 °C and 65°C. After completion of the reaction, the reaction mixture is

added to water, the solution is extracted, for example, with diethyl ether, dichloromethane, chloroform, methyl tert-butyl ether or tetrahydrofuran and the organic phase obtained in each case is dried using anhydrous sodium sulfate. The organic phase is concentrated in vacuo, the residue which remains is crystallized by trituration or the oily residue is purified by recrystallization, distillation or by column or flash chromatography on silica gel or alumina. The eluent used is, for example, a mixture of dichloromethane and diethyl ether in the ration 8:2 (vol/vol) or a mixture of dichloromethane and ethanol in the ration of 9:1 (vol/vol).

2nd Stage

The N-substituted indole obtained by the abovementioned 1st stage procedure is dissolved under a nitrogen atmosphere in an aprotic or nonpolar organic solvent, such as, for example, diethyl ether, methyl tert-butyl ether, tetrahydrofuran, dioxane, toluene, xylene, methylene chloride or chloroform and added to a solution, prepared under a nitrogen atmosphere, of a simply molar up to 60 percent excess amount of oxalyl chloride in an aprotic or nonpolar solvent, such as, for example, in diethyl ether, methyl tert-butyl ether, tetrahydrofuran, dioxane, toluene, xylene, methylene chloride or chloroform, the temperature being kept between -5 °C and 20 °C. The reaction solution is then heated at a temperature between 10 °C and 130 °C, preferably between 20 °C and 80 °C, particularly between 30 °C and 50 °C, for a period of 30 minutes up to 5 hours and the solvent is then evaporated. The residue of the indolyl-3-glyoxylic acid chloride formed in this manner which remains dissolved in an aprotic solvent such as, for example, tetrahydrofuran, dioxane, diethyl ether, toluene or alternatively in a dipolar aprotic solvent, such as, for example, dimethylformamide, dimethylacetamide or dimethyl sulfoxide, cooled to a temperature between 10 °C and -15 °C, preferably between -5 °C and 0 °C, and treated in the presence of an acid scavenger with a solution of the primary or secondary amine in a diluent.

Possible diluents are the solvents used above for the dissolution of the indolyl-3-glyoxylic acid chloride. Acid scavengers used are triethylamine, pyridine, dimethylaminopyridine, basic ion exchanger, sodium carbonate, potassium carbonate, powdered potassium hydroxide and excess primary or secondary amine employed for the reaction. The reaction takes place at a temperature

from 0 °C to 120 °C, preferably at 20 °C to 80 °C, particularly between 40 °C and 60 °C. After a reaction time of 1 to 3 hours and standing at room temperature for 24 hours, the hydrochloride of the acid scavenger is filtered, the filtrate is concentrated in vacuo, and the residue is recrystallized from an organic solvent or purified by column chromatography on silica gel or alumina. The eluent used is, for example, a mixture of dichloromethane and ethanol (95:5, vol/vol).

Please amend the paragraph beginning on page 9, line 1 as follows:

- in various models, it was not possible to find any neurotoxicity with the N-substituted indole-3-~~gloxylamides [sic]~~glyoxylamides according to claim 1 ~~general formula 1a~~ in contrast to most antitumor preparations.

Please amend the paragraph beginning on page 9, line 11 as follows:

1. The cytotoxic activity of D-24851 (~~see claim 4~~N-(pyridin-4-yl)-[1-(4-chlorobenzyl)-indole-3-yl]glyoxylamide) on the MDR (multidrug-resistant) leukemia cell line of the mouse L 1210/VCR is not ~~influenced~~ altered in vivo ~~and~~ or in vitro. See Figures 1, 2 and 3.

Please amend the paragraph beginning on page 9, line 16 as follows:

D-24851 ~~(see claim 4)~~ has an unchanged cytotoxic activity against the multidrug-resistant mouse leukemia cell subline L1210/VCR in contrast to Taxol, ~~doxirubicin~~doxorubicin, vincristine, or ~~epothilone~~ epothilone B ~~[sic]~~.

Please amend the paragraphs beginning on page 9, line 23 as follows:

The mouse leukemia cell ~~lines [sic]~~line L 120 was adapted to vincristine. The unadapted (L 1210) and the adapted (L 1210/VCR) cells were exposed to cytostatic agents and the cell growth, which was determined by the metabolic activity, was determined (XTT test). The curves which connect the XTT datapoints were calculated using a nonlinear regression program. These

experimental results were also confirmed in vitro on the human resistant LT 12/MDR cell line (see Figure 4).

2. The detection of ~~lacking~~ lack of metastasis formation was afforded by means of inhibition of migration of MO4 cells. See Figure 5. D-24[[ ]]851 ~~(see claim 4)~~ inhibits the migration of MO4 cells in a dose-dependent manner. From this, an anti-invasive and an anti-metastatic action can be derived for D-24851.

Please amend the paragraph beginning on page 10, line 22 as follows:

3. From comparison experiments of the compound according to the invention D-24851 ~~(see claim 4)~~ with vincristine and Taxol on rats, where ataxia, traction and reaction were assessed (see Figure 6), it is evident that this compound shows no neurotoxic effect, in contrast to Taxol and vincristine. Furthermore, in comparison to Taxol and vincristine, D-24851 has no negative influence on the nerve conduction velocity (see Figure 7). This confirms that D-24851, on account of the ~~absent~~ absence of neurotoxicity, has clearly lower side effects than other chemotherapeutics.

Please amend the paragraph beginning on page 10, line 35 as follows:

4. From further investigations as shown in Figures 8 and 9, it is evident that the compound D-25851 (~~see claim 4~~ N-(pyridin-4-yl)-[1-(4-chlorobenzyl)-indole-3-yl]glyoxylamide) has a potential as an angiogenesis inhibitor. As a result of the physiological relationship with tumor growth, angiogenesis inhibitors are simultaneously also agents for the inhibition of tumor growth, in that the formation of new blood vessels, which are intended to feed the tumor, is inhibited. In vitro in an angiogenesis model on endothelial cells, D-24851 causes a complete inhibition of vascularization, which is not based on a cytotoxic effect. It can be seen in Figure 8 that D-24851 almost completely breaks up existing cell-cell contacts due to 0.1 µM~~ol/l~~ L of D-24851 ~~[sic]~~ (see vital staining). Normally, the cells maintain at least partial contact. Cell migration is markedly reduced, many cells are rounded. Lethal staining in a monolayer before angiogenesis induction did not show any increased cell mortality with D-24851. Even in the first 22 hours after induction, no

increased cell mortality was yet discernible in comparison with the control[[.]] (~~See~~ see lethal staining in Figure 9, white points).

Please amend the paragraph beginning on page 11, line 37 as follows:

Without wanting to restrict the scope of the invention by the following statements, it can be said that doses from about 20 mg up to 500 mg daily are possible orally. On intravenous administration as an injection or as an infusion, up to 250 mg/day or more can be administered depending on the body weight of the patient and individual tolerability. As a result of the ~~lacking~~ lack of development of resistance and suppression of metastasis, a high effectiveness and wide use of the agents ~~for [sic]~~ even in tumor-refractory patients can be expected. The antiangiogenesis effect is suitable for additionally suppressing the spread of the tumor. However, the invention also comprises the use of the N-substituted indole-3-~~gloxylamides [sic]~~glyoxylamides according to claim 1 ~~general formula 1a~~ in further disorders in which an angiogenesis inhibitory effect is functionally desired[[.]] (e.g. wound healing). In addition, the invention also relates to the fixed or free combination of the N-substituted indole-3-~~gloxylamides [sic]~~glyoxylamides according to claim 1 ~~general formula 1a~~ with antitumor agents known per se, and also the replacement of antitumor agents which have become ineffective as a result of resistance development by N-substituted indole-3-~~gloxylamides [sic]~~glyoxylamides according to claim 1 ~~general formula 1a~~.